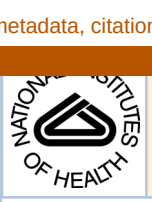

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Examining the Motor Phenotype of Patients with Both Essential Tremor and Parkinson's Disease

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Abstract

Background—The subset of patients with essential tremor (ET) that develops Parkinson's disease (PD) has not been fully clinically characterized.

Methods—Motor features were retrospectively reviewed in 18 ET patients who developed PD (ET→PD), 20 ET and 30 PD patients with similar ages and disease durations.

Results—Fewer ET→PD than ET patients had widespread postural and/or action tremor (2/17 [11.8%] vs. 11/17 [64.7%]; p = 0.001) and marginally fewer had cerebellar signs (1/15 [6.7%] vs. 6/18 [33.3%], p = 0.06). ET→PD patients required fewer ET medications than did their counterparts with ET (p = 0.001). ET→PD patients and PD patients did not differ in UPDRS, Hoehn and Yahr, or Schwab and England scores (each p≥0.14).

Discussion—ET patients who develop PD may have distinct pre-PD motor features compared to their counterparts with ET who do not develop co-existing PD. Prospective studies are needed to evaluate the predictive value of these clinical features for the emergence of PD.

Keywords

Essential tremor; Parkinson's disease; tremor severity

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Introduction

Evidence supports an association between Parkinson's disease (PD) and essential tremor (ET).[1–3] A subset of ET patients might be at higher risk of developing PD;[2, 4] however, this subset has yet to be fully clinically characterized. The aim of these retrospective analyses was to determine whether patients with both ET and PD (ET→PD) are clinically distinct from ET patients in terms of certain motor features. Our hypothesis was that ET→PD patients would have less severe action tremor than ET patients. Also, previous studies[2, 5] have suggested that the PD phenotype in ET→PD patients is less severe than that of PD patients. We compared ET→PD patients with PD patients to explore this issue as well. The overarching goal of these analyses was to use these clinical data to further refine our understanding of the subset of ET patients who are at risk of developing PD.

Methods

Patient selection

The clinical database of the Movement Disorder Program of University of Louisville, KY, was used for the current analyses, which were centered on three patient groups: 1) PD with previous diagnosis of ET (ET→PD), 2) ET without PD (ET), and 3) PD without ET (PD). Searching for the words "Parkinson" and "tremor" retrieved 387 and 110 patients, respectively. Of these, 319 and 64 charts, respectively, were available. These charts were reviewed by a fourth year neurology resident (R.M.S), with special interest and training in Movement Disorders, to locate patients with both the diagnosis of PD (meeting UK Parkinson's disease Brain Bank criteria[6] for probable PD) and a previous history of ET (fulfilling criteria of definite ET according to the consensus statement of the Movement Disorder Society,[7] if parkinsonian signs were not considered): 18 were identified. Although no minimum time between ET and PD onset was specified, all but two patients had latencies ≥5 years. Based on the observed age distribution of the 18 ET→PD patients, ET patients and PD patients were selected if ≥60 years old, in order to ensure age comparability among groups. Similarly, PD duration in the PD group was restricted to ≤5 years in order to ensure comparability of PD duration with ET→PD patients.

Seventy-four of the "Parkinson" charts reviewed met the above inclusion criteria for the PD group (≥60 years old, ≤5 years of PD and UK Parkinson's disease Brain Bank criteria[6] for probable PD), and the first 30 on an alphabetical list were selected. Of the 64 "tremor" charts reviewed, 20 fulfilled inclusion criteria for the ET group (age ≥60 years old, definite ET according to the consensus statement of the Movement Disorder Society[7]) and all 20 were selected.

Data abstraction

All clinical charts were reviewed (R.M.S.), and every third chart was also reviewed by a movement disorder neurologist (A.C.) to ensure that abstracted data were valid. To assess reviewer bias, a third reviewer (E.G., a physician who was a research assistant in the Movement Disorders division), who was blinded to the study hypothesis, reviewed a random sample of 10 ET→PD patient charts, assessing the main findings (anatomic distribution of tremor and number of ET medications). There was high agreement between reviewers, indicating that reviewer bias was not present. A data abstraction form included self-reported family history (first-degree relatives) of ET or PD, age at onset (based on first symptom) of PD and ET, and first parkinsonian symptom, as well as data from the most recent visit. Data from the most recent visited included age, anatomic distribution of tremor (upper and lower limb postural and kinetic tremors, head tremor, and voice tremor, based on both history and examination), ET medications, and data from the neurological examination. Other objective

data from the most recent visit included cerebellar signs, subscores of the motor Unified Parkinson's Disease Rating Scale[8] (UPDRS) (rest tremor, rigidity, bradykinesia, postural instability), total UPDRS score, Hoehn and Yahr score,[9] and Schwab and England[10] score. Cerebellar signs were coded as present if any of nystagmus, intention tremor or dysmetria in the finger-to-nose or heel-to-knee maneuvers were present. Rest tremor, bradykinesia, rigidity, and postural instability (pull test) were coded as present when the UPDRS score was ≥1. Widespread postural and/or action tremor indicated that tremor was not restricted to the arms but also included the head, voice, or legs. To compare ET→PD and PD patients, the highest UPDRS subscores (right or left side) were used.

Data analyses

Statistical analysis was performed using the SPSS 10 (R.M.S.). Parametric tests were used throughout (Chi-square test for categorical variables and t-test or ANOVA for continuous variables). Statistical significance was considered when $p<0.05$.

Results

Demographics (Table 1)

ET→PD, ET and PD patients had similar gender and age.

ET→PD vs. ET (Table 1)

ET→PD and ET patients had similar duration of ET. Fewer ET→PD patients had widespread postural and/or action tremor at their most recent visit, especially head tremor. Marginally fewer ET→ PD had cerebellar signs than did their counterparts with ET. ET→PD patients required fewer ET medications at their most recent visit than did their counterparts with ET. Family history of PD was nearly twice as common in ET→PD, but the difference was not significant. As expected, signs of parkinsonism were more common in ET→PD than ET patients.

One could argue that, after receiving a diagnosis of PD, ET symptoms and signs in ET→PD patients might receive less attention (i.e., not commented on in clinical notes and not the focus of treatment efforts). To assess this possibility, we performed sensitivity analyses. ET→PD cases were stratified into two groups (mild PD vs. more severe PD) based on the median UPDRS score. We hypothesized that the presence of fewer ET signs in the group with more severe PD would support the notion that PD signs were drawing attention away from ET signs. By contrast, similar severity of ET in the two groups would argue that PD signs were not drawing attention away from ET signs. We found that a similar proportion of ET cases in each group had widespread postural and/or action tremor ($p = 0.72$) and a similar proportion of ET cases in each group required more than one medication ($p = 0.56$).

ET→PD vs. PD (Table 1)

The latency between ET and PD onset was 19.3±15.7 (range 2–64) years. The majority (61.1%, 11/18) had a latency >10 years and, in 11.1% (2/18) it was <5 years. The main PD phenotypes in the PD group were tremor predominant or mixed tremor–bradykinesia–rigidity (75.9%; 22/29). Family history of ET was more common in ET→PD than PD patients. UPDRS scores were similar in the two groups.

Discussion

ET patients are more likely to develop PD than controls[11] and there is growing clinical,[1, 2, 4] imaging,[12–14] and neuropathological[15–17] evidence supporting a physiopathological link between ET and PD.

In this study, fewer ET→PD patients had widespread postural and/or action tremor or cerebellar signs and they required fewer ET medications than did their counterparts with ET. The duration of ET was similar in these ET→PD and ET patients. One possible explanation is that ET patients who are prone to developing PD have a less severe ET phenotype than do their counterparts who do not develop PD. An alternative explanation, which we cannot fully exclude, is that, after receiving a diagnosis of PD, ET symptoms and signs in ET→PD patients received less attention (i.e., not commented on in clinical notes and not the focus of treatment efforts). However, our sensitivity analyses suggested that this was not the case.

ET→PD patients have previously been shown to have less severe parkinsonism[2, 5] when compared to other PD patients. This was not noted in the current dataset. This difference could be due to our small sample size, retrospective design, short duration of PD (less than 5 years), and high proportion of PD patients with non-akinetic rigid phenotypes, which are known to have a better motor outcome.[18, 19]

This study has some limitations. First, the retrospective design and the small sample size may have limited the power to detect associations. It is possible that some group differences were only detected as trends rather than statistically significant differences. This being said, many significant associations were detected, indicating that the sample size was adequate for those comparisons. Second, limb postural, and kinetic tremors, head tremor, and voice tremor were assessed during routine clinical care; however, a standardized, ordinal tremor rating scale was not used; this may have biased the results towards the null hypothesis by reducing precision and obscuring differences between ET groups that may have been present.

In summary, our study suggests that ET patients who develop PD may have distinct pre-PD motor features than their counterparts with ET who do not develop co-existing PD. Prospective studies are now needed to evaluate the predictive value of these clinical features for the emergence of PD.

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Table 1

Comparison of Demographic Characteristics and Motor Features of ET→PD, ET, and PD Patients

	ET → PD (n = 18)	ET (n = 20)	PD (n = 30)	Significance (p)
Demographic characteristics				
Age at last visit (mean ± SD years)	74.4 ± 8.2	72.8 ± 8.1	71.0 ± 7.3	0.34[1]
Gender (males: n; %)	13; 72.2%	11; 55.0%	21; 70.0%	0.45[3]
ET → PD vs. ET				
Age at onset of ET (mean ± SD years)	49.8 ± 18.6	47.6 ± 24.8	–	0.75[2]
Duration of ET (mean ± SD years)	24.0 ± 15.6	25.4 ± 21.6	–	0.82[2]
Duration of ET prior to PD onset (mean ± SD years)	19.3 ± 15.7	–	–	–
Family history of ET (n; %)	9/17; 52.9%	11/20; 55.0%	–	0.90[3]
Family history of PD (n; %)	3/17; 17.6%	2/20; 10.0%	–	0.50[3]
Rest tremor (n; %)	13/16,81.2%	5/19; 26.3%	–	<0.001[3]
Bradykinesia (n; %)	11/12,91.7%	3/18; 16.7%	–	<0.0001
Rigidity (n; %)	11/12,91.7%	5/19; 26.3%	–	<0.0001
Postural instability (n; %)	4/16; 25.0%	1/17; 5.9%	–	0.13[3]
Cerebellar signs (n; %)	1/15,6.7%	6/18, 33.3%	–	0.06[3]
Widespread postural and/or action tremor (n; %)	2/17; 11.8%	11/17; 64.7%	–	0.001[3]
Lower limb tremor (n; %)	1/17; 5.9%	4/17; 23.5%		0.15[3]
Head tremor (n,%)	1/17; 5.9%	7/17; 41.2%		0.02[3]
Voice tremor (n, %)	2/17; 11.8%	4/17; 23.5%		0.37[3]
Need > 1 medication for ET at most recent visit (n; %)	2/17; 11.8%	12/18; 66.7%	–	0.001[3]
ET → PD vs. PD				
Age at onset of PD (mean ± SD years)	71.4 ± 10.1	–	67.7 ± 7.0	0.14[2]
Duration of PD (mean ± SD years)	4.8 ± 7.6	–	3.8 ± 4.2	0.56[2]
Family History of ET (n, %)	9/17; 52.9%	–	2/24; 8.3%	<0.0001[3]
Family history of PD (n; %)	5/17; 29.4%	–	7/29; 24.1%	0.80[3]
First symptom of PD				

	ET → PD (n = 18)	ET (n = 20)	PD (n = 30)	Significance (p)
Rest tremor (n; %)	8/15; 53.3%	–	19/27; 70.4%	0.18[3]
Bradykinesia (n; %)	7/15; 46.7%	–	6/27; 22.2%	
Rigidity (n; %)	0/15; 0%	–	2/27; 7.4%	
UPDRS – rest tremor upper limb (mean ± SD)[2]	1.3 ± 1.0[4]	–	1.0 ± 1.0[4]	0.25[2]
UPDRS – finger tapping (mean ± SD)[5]	1.1 ± 0.7[4]	–	1.5 ± 0.7[4]	0.10[2]
UPDRS – rigidity upper limb (mean ± SD)	1.1 ± 0.5[4]	–	1.4 ± 0.6[4]	0.10[2]
UPDRS – pull test (mean ± SD)	0.5 ± 0.6[4]	–	0.2 ± 0.4[4]	0.25[2]
UPDRS total (mean ± SD)	22.4 ± 14.8[4]	–	30.4 ± 17.6[4]	0.14[2]
Hoehn and Yahr score (mean ± SD)	2.2 ± 0.7	–	2.0 ± 0.4	0.22[2]
Schwab and England score (mean ± SD)	91.8 ± 7.2[4]	–	87.9 ± 8.7[4]	0.15[2]

% are related to the available data;

Statistical tests used:

[1]ANOVA,

[2]t-test, and

[3]Chi-square.

[4]Data not available for all subjects

[5]Data from most affected side (right or left) were used.

Abbreviations: ET, essential tremor; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.